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Does tramadol have a place in the dental armamentarium? An atypical opioid in dental practice from the pharmacological perspective – Part II. Local tramadol administration within orofacial tissues

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ABSTRACT
Tramadol is the most widely used analgesic in the world. Indications for the general administration of tramadol in dentistry and oral surgery are restricted to cases with moderate to severe pain. However, new evidence supports the peripheral use of this well-known drug. The unique properties of this atypical opioid, including its impact on neuronal conduction, attenuation of inflammation, and antimicrobial effects, together with its possible beneficial influence on the wound healing process, have been observed after local administration in human and animal research. The paper focuses on the local administration of tramadol within orofacial tissues, with particular consideration given to its possible use in dentistry.
Keywords: tramadol; pain management; dentistry; oral surgery.

INTRODUCTION

The indications for general administration in dentistry are restricted to cases with moderate to severe pain, as discussed in previous work [1]. However, the drug may also be administered locally, and the mounting evidence of promising results obtained from human and animal research encourages the consideration of local administration in various clinical situations. This paper focuses on the local administration of tramadol within orofacial tissues, with a particular emphasis on its potential use in dentistry.

RATIONALE BEHIND THE LOCAL TRAMADOL ADMINISTRATION

Tramadol, (±)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol, is an atypical opioid agent with additional properties that make it a valuable tool in pain management. The drug's unique attributes encourage its utilization in medicine and dentistry [1]. The impact of this atypical opioid on various mechanisms, such as neuronal conduction, inflammatory mediators, and macrophage polarization justifies its local administration and a growing body of evidence supports this strategy within orofacial tissues [2, 3]. Two highly important factors that contribute to the efficacy of this approach are its local anesthetic action resulting from Na^+ and K^+ channel block, and its ability to attenuate peripheral inflammatory reactions [2].

Furthermore, after local administration, the medicine exhibits an antimicrobial effect specifically against *Pseudomonas aeruginosa* and *Staphylococcus aureus* [4]. Observations have also been made regarding the dose- and time-dependent bactericidal activity of tramadol against *Escherichia coli* and *Staphylococcus epidermidis* [5]. The proposed mechanism of the antimicrobial action of this atypical opioid is based on the depolarization and permeabilization of the outer membrane of Gram– bacteria, as well as the inactivation of enzymes bound to the membrane in the case of Gram+ species [6].

In animal studies on wound healing, tramadol infiltration prior to the buccal incision has demonstrated a beneficial impact on the wound healing process and resulted in a significant reduction in colony-forming units of oral microorganisms [7]. It is noteworthy that further research is needed to investigate the possible positive influence of local tramadol on oral mucosa healing. This is particularly interesting, considering the tramadol-induced oxidative damage and apoptosis in oral tissues observed after the general administration of high tramadol doses in animal models [8].

The impact of local tramadol on the wound healing process in the oral cavity, as well as its exact antimicrobial effect, has not been thoroughly investigated in humans. However, recent animal studies on the local tramadol administration in orofacial tissues have provided valuable insights that pave the way for further research in humans and potential utilization in clinical practice. These studies are presented in Table 1.

TABLE 1. Local tramadol administration within orofacial tissues – animal models of clinical significance in clinical practice

Clinical situation in humans	Animal model	Tramadol dose and formula used	Results
Oral wound healing	buccal mucosal incision in a rabbit	0.5 mL of 100 mg/2mL solution in submucosal injection in the side of procedure	in comparison with control groups (saline and lidocaine submucosal infiltration): faster epithelialization and wound healing, significant reduction of CFU of oral microorganism from the region of the wound
TMJ osteoarthritis	formalin-induced TMJ nociception in a rat, capsaicin-induced TMJ nociception in a rat, carrageenan-induced TMJ hypernociception in a rat, 5-HT – induced TMJ hypernociception in a rat	500 µg in intraarticular injection either together with a provoking agent (formalin, capsaicin) or as a pre-treatment (15 min before carrageenan or 5-HT intraarticular injection)	peripheral antinociceptive effect together with local anti-inflammatory action in the side of administration

5-HT – 5-hydroxytryptamine (serotonin); CFU – colony-forming units; TMJ – temporomandibular joint

LOCAL TRAMADOL – POSSIBLE USE IN DENTISTRY

The direct application of an analgesic to the source of pain allows for immediate higher concentrations at the site, while maintaining lower systemic drug levels and reducing the occurrence of side effects [9]. In contrast to general administration, the early analgesic effect of local tramadol is achieved through the parent drug rather than the active metabolite (O-desmethyltramadol, also known as M1), making it largely independent of cytochrome P450 2D6 (CYP4502D6) genetic polymorphism [10, 11].

Within orofacial tissues, tramadol can be administered topically or through submucosal and intra-articular injections. Recent investigations in humans have explored various methods of local tramadol administration in the oral cavity and adjacent tissues, along with the clinical situations in which such a strategy may be beneficial in dental practice. These findings are listed in Table 2.

The topical application of tramadol solution on the mucosa has been proven to be a valuable aid for practitioners. Application of tramadol-soaked swabs to the tonsillar fossa has shown improvements in symptoms after tonsillectomy [12, 13]. Similar findings were obtained in oral surgery, where tramadol solution placed in extraction sockets on resorbable gelatine sponges proved effective in managing postprocedural pain after mandibular molar extractions [14]. Additionally, the use of tramadol solution as a gargle has alleviated postoperative sore throat, while 5% tramadol gel has been found to be equally effective as 2% lidocaine in preventing complications of orotracheal intubation [15, 16].

These observations encourage further research into the potential use of tramadol gargle and gel in conditions affecting the oral mucosa, such as stomatitis.

Intra-articular injection of tramadol has been shown to provide adequate analgesia in arthroscopic knee surgery and an animal model of joint inflammation [2]. These results inspire the consideration of a similar strategy in temporomandibular

TABLE 2. Local tramadol administration within orofacial tissues – ways of application and possible clinical use in dentistry

Way of administration	Tramadol formula used	Place of administration	Clinical situation in dentistry
Topical	5% solution administered as gargle, on swabs soaked with solution, and gelatine resorbable sponges (intrasocket)	oral mucosa, postextractional sockets	early management and prevention of postprocedural pain in oral surgery, after exodontia, symptomatic management of oral mucositis and other painful conditions (further research needed)
Intraarticular injection	50 mg from 5% solution diluted with 5% Ringer's lactate	TMJ – administered after arthrocentesis	temporomandibular osteoarthritis
Submucosal injection	5% solution, 5% solution with epinephrine 1:80,000	close proximity to surgical intervention (performed or planned), near sensory nerve trunk or nerve endings	postprocedural pain management in oral surgery, preemptive analgesia, improvement of efficacy of IANB in symptomatic patients, infiltrative and block local anesthesia (plain, with epinephrine or as adjunct to local anesthetic solution)

IANB – inferior alveolar nerve block; TMJ – temporomandibular join

joint (TMJ) disorders, particularly because intra-articular tramadol has been observed to exhibit anti-inflammatory action in a rat model of TMJ inflammation [17].

Intraarticular injection of tramadol solution in the TMJ, following joint aspiration has demonstrated an acceptable analgesic effect. This effect, although less potent than morphine, has been found to be longer-lasting [18]. Both agents, when administered through this route after arthrocentesis, show a high probability of being the optimal strategy for pain management in temporomandibular osteoarthritis [19].

Tramadol solution can also be administered in the oral cavity through submucosal injection. It has been found that submucosal tramadol is superior and more effective in reducing pain after minor oral surgical procedures compared to the same dose injected intramuscularly [20]. In third molar surgery, a better outcome was achieved with a combination of both routes of administration [21].

Local administration of tramadol to the surgical site, in addition to a systemic dose, may prolong the duration of the anesthetic effect and improve the quality of postoperative analgesia following other dentoalveolar surgery procedures [22, 23, 24]. Tramadol solution administered via submucosal injection in close proximity to the planned intervention can be a significant component of pre-emptive analgesia strategy in oral surgery, in addition to an oral non-steroidal anti-inflammatory drug, such as ibuprofen [25].

Similarly, in conservative dentistry, submucosal injection of tramadol prior to inferior alveolar nerve block (IANB) in patients with irreversible symptomatic pulpitis has facilitated successful anesthesia and proved to be an effective strategy in postoperative pain management after root canal treatment in mandibular molars [26, 27].

TRAMADOL IN LOCAL ANESTHESIA

The addition of tramadol local anesthetic solution has been shown to improve their efficacy. In medicine, the drug is used with varying success as an adjunct to local anesthetics for a neuraxial blockade via intrathecal, epidural, or combined spinal-epidural approach [28]. Tramadol has also been utilized with local anesthetics for regional blocks, such as those performed in the upper extremities [29].

Similar attempts have been made in dentistry. Since IANB is often challenging for practitioners, several trials have investigated whether tramadol could be a valuable adjunct in this specific procedure. The addition of tramadol to articaine has been found to improve the duration of IANB obtained in oral surgery [30]. However, in patients with symptomatic irreversible pulpitis of mandibular molars, adding tramadol to a mepivacaine solution did not improve the success rate of the performed IANB [31].

Tramadol's impact on voltage-gated Na+ and K+ channels is responsible for its local anesthetic qualities [2]. In contrast to the parent drug, its main metabolite, M1, does not affect sensory nerve conduction [10]. The local anesthetic properties of 5% tramadol solution enable its use as a standalone agent. Pang et al. were the first to report that intradermal administration of 25 mg tramadol provides effective anesthesia in preventing pain caused by propofol injection. The authors observed that intradermal tramadol administration had a similar effect to prilocaine and could be used in skin excision [32]. Promising outcomes encouraged further research on the possible use of tramadol as a local anesthetic within the oral cavity.

The local anesthetic effect of plain tramadol was found to be similar to lignocaine when injected as infiltration in oral soft tissues [33]. In simple extractions in the maxilla, the local anesthetic effect of infiltrative supra-periosteal injections of tramadol allowed for successful completion of procedures, with comparable or slightly weaker efficacy compared to 2% lidocaine both plain or with epinephrine in a 1:100,000 dilution [34, 35, 36, 37]. The differences in the onset of action were insignificant, but the duration of tramadol effect was shorter. However, the analgesic properties of the drug provided lower scores of post-operative pain intensity [38]. Tramadol's dilation of blood vessels at the injection site further impairs its expected local action [39, 40]. The addition of a vasoconstrictor, such as epinephrine, helps confine tramadol locally, enabling it to produce its effects on the nerve more effectively [40]. Favourable results were obtained after using tramadol with epinephrine (dilution 1:200,000) in minor surgery procedures in dermatology, leading to similar attempts in the field of oral surgery [40, 41]. The epinephrine dilution used with tramadol in oral surgery was lower, specifically 1:80,000, which means that in 1.8 mL of solution, 0.0225 mg of epinephrine was present. This combination in infiltrative local anesthesia in maxilla was more effective that plain tramadol and showed equal efficacy to 2% lidocaine with 1:80,000 epinephrine, and allowed for exodontia of maxillary teeth [40, 42, 43, 44]. The duration of anesthetic action of tramadol with epinephrine was shorter than that of lidocaine with epinephrine, but once again, it provided more pronounced post-procedural analgesia [40, 42, 43, 44]. One study additionally reportedbetter socket healing after extraction in the tramadol-epinephrine group compared to patients from the lidocaine-epinephrine group [43]. Tramadol with epinephrine was proven to be an effective tool in IANB as well, providing local anesthesia similar to lidocaine with epinephrine, with a shorter duration but comparable efficacy. This allowed for oral surgery procedures involving oral mucosa incision and bone removal, such as impacted teeth extraction, surgical exodontia, and apicoectomy [45].

Trials in which tramadol was administered as a local anesthetic in dental procedures have reported possible adverse effects, including nausea (4.6%), dizziness (1.3%), vomiting (0.7%), and local erythema (0.4%). While these effects are not severe, they do limit the use of tramadol as a local anesthetic in this field [46].

The excellent safety, efficacy, and established history of aminoamide anesthetics contribute to their widespread use in everyday dental practice. Instead of being a replacement for conventional local anesthetics, tramadol serves as an alternative in rare cases when the use of routine local anesthetics

is contraindicated, especially when postprocedural pain is expected [46].

Tramadol with epinephrine presents an interesting option in local anesthesia in dentistry, providing postoperative analgesia independently of its short anesthetic effect, which is a definite advantage. The alleviation of post-operative pain without motor blockade distinguishes local tramadol from long-acting local anesthetics, such as bupivacaine and ropivacaine, typically used in oral surgery. Therefore, its application for procedures in the mandible, specifically, holds great appeal [47].

SUMMARY

Tramadol hydrochloride, an atypical opioid agent, demonstrates an unconventional mechanism of analgesia. While general tramadol is not typically the preferred choice for managing pain in dentistry and oral surgery due to its characteristics, local administration in dental practice may present a viable strategy. Accumulating evidence from both animal and human trials supports its local anesthetic and analgesic effects, along with the potential to reduce inflammation and positively influence wound healing within orofacial tissues. The results obtained in the trials conducted in recent trials encourage further research in this field and open up new possibilities for utilizing this well-known drug in oral surgery.

REFERENCES

1. Pasternak M. Does tramadol have a place in the dental armamentarium? An atypical opioid in dental practice from the pharmacological perspective – Part I. General tramadol administration. Pomeranian J Life Sci 2023;69(1):30-8. doi: 10.21164/pomjlifesci.901.
2. Barakat A. Revisiting tramadol: a multi-modal agent for pain management. CNS Drugs 2019;33(5):481-501.
3. Danić P, Salarić I, Macan D. New findings on local tramadol use in oral surgery. Acta Stomatol Croat 2017;51(4):336-44.
4. Farzam H, Farahani A, Tafkik A, Gorgin Karaji A, Mohajeri P, Rezaei M, et al. Antibacterial effect of tramadol against *Staphylococcus aureus* and *Pseudomonas aeruginosa*: an *in vivo* study. New Microbes New Infect 2018;24:42-6. doi: 10.1016/j.nmni.2018.04.001.
5. Tamanai-Shacoori Z, Shacoori V, Jolivet-Gougeon A, Vo Van JM, Repère M, Donnio PY, et al. The antibacterial activity of tramadol against bacteria associated with infectious complications after local or regional anesthesia. Anesth Analg 2007;105(2):524-7.
6. Al-Kurashy H, Ismail A, Al-windy S. Bacteriostatic effects of tramadol. In: Proceeding of 3rd scientific conference of the College of Science, University of Baghdad. Baghdad: University of Baghdad; 2009. p. 911-5.
7. Al-Mashhadane FA, Mustafa EA, Taqa GA. Histological and antimicrobial effects of tramadol infiltration on incisional oral mucosal wound healing in rabbits. Iraqi J Veterinary Sci 2019;33(2):335-40.
8. Hassabou NF, Elseweidy MM. Histopathological changes in submandibular gland and dorsal tongue of experimental rats due to prolonged tramadol intake focusing on novel modulatory effect of 10-dehydrogingerdione. Arch Oral Biol 2021;130:105223. doi: 10.1016/j.archoralbio.2021.105223.
9. Bolaños DC, Guillén AP. Peripheral Tramadol in Dentistry: A New Use for an Old Drug Tramadol periférico en odontología: Un nuevo uso para un medicamento antiguo. Odovtos-International J Dental Sci 2016;18(2):10-4.
10. Katsuki R, Fujita T, Koga A, Liu T, Nakatsuka T, Nakashima M, et al. Tramadol, but not its major metabolite (mono-O-demethyl tramadol) depresses compound action potentials in frog sciatic nerves. Br J Pharmacol 2006;149(3):319-27.
11. Sousa AM, Ashmawi HA. Local analgesic effect of tramadol is not mediated by opioid receptors in early postoperative pain in rats. Rev Bras Anestesiol 2015;65(3):186-90.
12. Akbay BK, Yildizbas S, Guclu E, Yilmaz S, Iskender A, Ozturk O. Analgesic efficacy of topical tramadol in the control of postoperative pain in children after tonsillectomy. J Anesth 2010;24(5):705-8.
13. Tekelioglu UY, Apuhan T, Akkaya A, Demirhan A, Yildiz I, Simsek T, et al. Comparison of topical tramadol and ketamine in pain treatment after tonsillectomy. Pediatric Anaesth 2013;23(6):496-501.
14. Gönül O, Satilmiş T, Ciftci A, Sipahi A, Garip H, Göker K. Comparison of the effects of topical ketamine and tramadol on postoperative pain after mandibular molar extraction. J Oral Maxillofac Surg 2015;73(11):2103-7.
15. Farzam H, Yari M, Mohammadi G, Rahmatinejad M. A comparative study of tramadol and lidocaine gel on complications of orotracheal intubation. Anesth Pain Intens Care 2020;24(2):183-8.
16. Rashwan S, Abdelmawgoud A, Badawy AA. Effect of tramadol gargle on postoperative sore throat: a double blinded randomized placebo controlled study. Egypt J Anesth 2014;30(3):235-9.
17. Lamana SMS, Napimoga MH, Nascimento APC, Freitas FF, de Araujo DR, Quinteiro MS, et al. The anti-inflammatory effect of tramadol in the temporomandibular joint of rats. Eur J Pharmacol 2017;807:82-90.
18. Sipahi A, Satilmis T, Basa S. Comparative study in patients with symptomatic internal derangements of the temporomandibular joint: analgesic outcomes of arthrocentesis with or without intra-articular morphine and tramadol. Br J Oral Maxillofac Surg 2015;53(4):316-20.
19. Liu Y, Wu JS, Tang YL, Tang YJ, Fei W, Liang XH. Multiple treatment meta--analysis of intra-articular injection for temporomandibular osteoarthritis. J Oral Maxillofac Surg 2020;78(3):373.e1-e18.
20. Rejab AF. Comparison of the intramuscular and sub-mucous postoperative analgesic effect of tramadol HCL after minor oral surgery. Int J Enhanc Res Sci Technol Eng 2014;3(5):122-9.
21. Pozos-Guillén Ade J, Martínez-Rider R, Aguirre-Bañuelos P, Arellano--Guerrero A, Hoyo-Vadillo C, Pérez-Urizar J. Analgesic efficacy of tramadol by route of administration in a clinical model of pain. Proc West Pharmacol Soc 2005;48:61-4.
22. Cillo JE. Peri-operative pain management in maxillofacial surgery. In: Ferneini EM, Bennett JD, editors. Perioperative assessment of the maxillofacial surgery patient. Cham: Springer; 2018. p.145-60. doi: 10.1007/978-3-319-58868-1_11.
23. Pozos AJ, Martínez R, Aguirre P, Pérez J. Tramadol administered in a combination of routes for reducing pain after removal of an impacted mandibular third molar. J Oral Maxillofac Surg 2007;65(8):1633-9.
24. Isiordia-Espinoza MA, Orozco-Solis M, Tobías-Azúa FJ, Méndez-Gutiérrez EP. Submucous tramadol increases the anesthetic efficacy of mepivacaine with epinephrine in inferior alveolar nerve block. Br J Oral Maxillofac Surg 2012;50(2):157-60.
25. Isiordia-Espinoza MA, Pozos-Guillén AJ, Martínez-Rider R, Herrera-Abarca JE, Pérez-Urizar J. Preemptive analgesic effectiveness of oral ketorolac plus local tramadol after impacted mandibular third molar surgery. Med Oral Patol Oral Cir Bucal 2011;16(6):e776-80. doi: 10.4317/medoral.16854.
26. Aksoy F, Ege B. The effect of pretreatment submucosal injections of tramadol and dexamethasone on post-endodontic pain in mandibular molar teeth with symptomatic irreversible pulpitis: a randomized controlled clinical trial. Int Endod J 2020;53(2):176-85.
27. De Pedro-Muñoz A, Mena-Álvarez J. The effect of preoperative submucosal administration of tramadol on the success rate of inferior alveolar nerve block on mandibular molars with symptomatic irreversible pulpitis: a randomized, double-blind placebo-controlled clinical trial. Int Endod J 2017;50(12):1134-42.
28. Fanelli D, Weller G, Liu H. New serotonin-norepinephrine reuptake inhibitors and their anesthetic and analgesic considerations. Neurol Int 2021;13(4):497-509. doi: 10.3390/neurolint13040049.
29. Shin HW, Ju BJ, Jang YK, You HS, Kang H, Park JY. Effect of tramadol as an adjuvant to local anesthetics for brachial plexus block: A systematic review and meta-analysis. PLoS One 2017;12(9):e0184649.
30. Pozos AJ, Martinez R, Aguirre P, Perez J. The effects of tramadol added to articaine on anesthesia duration. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102(5):614-7.
31. Rodríguez-Wong L, Pozos-Guillen A, Silva-Herzog D, Chavarría-Bolaños D. Efficacy of mepivacaine – tramadol combination on the success of inferior

alveolar nerve blocks in patients with symptomatic irreversible pulpitis: a randomized clinical trial. Int Endod J 2016;49(4):325-33.
32. Pang WW, Mok MS, Chang DP, Huang MH. Local anesthetic effect of tramadol, metoclopramide, and lidocaine following intradermal injection. Reg Anesth Pain Med 1998;23(6):580-3.
33. Jendi SK, Talathi A. Tramadol hydrochloride: an alternative to conventional local anesthetics for intraoral procedures – a preliminary study. J Oral Biol Craniofac Res 2019;9(1):111-4.
34. Basu S, Mukherjee O, Sahu S, Banerjee R, Pachisia S, Biswas A. Tramadol HCL as an effective alternative to lignocaine HCL for extraction of tooth under supraperiosteal infiltration. Indian J Dent Sci 2021;13(3):175-7.
35. Goel M, Sen P, Maturkar T, Latke S, Dehankar T. Effectiveness of tramadol compared to lignocaine as local anesthesia in the extraction of firm teeth: a randomized controlled trial. J Dent Anesth Pain Med 2021;21(3):245-52.
36. Jendi SK, Syed AM, Badal S, Doiphode A, Chougule SS, Shaikh SA, et al. Comparison of local anaesthetic efficacy of tramadol versus lignocaine for extraction of tooth under supraperiosteal infiltration. J Maxillofac Oral Surg 2019;18(1):100-5.
37. Ahmad Qureshi A, Mousa Bakri M. Comparative study of local anesthetic efficacy of 5% tramadol versus 2% lignocaine with 1:100,000 adrenaline for extraction of fully erupted maxillary 3rd molars using infiltration anesthesia. Saudi Dent J 2022;34(4):306-9.
38. Siva Kalyan U, Satya Bhushan NVV, Chiang KC, Aparna D, Sunil T. Efficacy of tramadol hydrochloride as local anaesthetic and analgesic agent for extraction of maxillary teeth. J Clin Diagnostic Res 2020;14(6):ZC26-30.
39. Shipton EA. Tramadol – present and future. Anaesth Intensive Care 2000;28(4):363-74.
40. Al-Haideri YA. Comparison of local anesthetic efficacy of tramadol hydrochloride (with adrenaline) versus plain tramadol hydrochloride in the extraction of upper molar teeth. J Oral Maxillofac Surg 2013;71(12):2035-8.
41. Kurdi MS, Ahmed Z, Mallikarjuna J. Tramadol-A local anesthetic with a difference. J Biomed Pharma Res 2014;3(2):49-54.
42. Srivastava M, Singh bedi R, Aurora J, Markandey AS, Vishal G. Comparison of local anesthetic efficacy of tramadol hydrochloride (with adrenaline) versus lignocaine hydrochloride (with adrenaline) in non-complicated tooth extractions. Intern J Appl Dent Sci 2018;4(3):243-6.
43. Ege B, Ege M, Koparal M, Alan H. Comparison of the anesthetic efficiency of lidocaine and tramadol hydrochloride in orthodontic extractions: a split-mouth, prospective, randomized, double-blind study. J Oral Maxillofac Surg 2020;78(1):52-62. doi: 10.1016/j.joms.2019.07.010.
44. Panda NK, Mishra S, Lenka S, Mandal S, Agastya H, Rathor K. Local anesthetic efficacy of tramadol hydrochloride with adrenaline in the extraction of maxillary teeth. J Biomed Pharmaceutical Res 2021;10(4):28-37.
45. Al-Haideri YA, Alsandook TA. A pilot double blinded clinical trial to compare between tramadol HCL and Lidocaine HCL as local anaesthesia amongst hospital-outpatient adult dental attendees Mosul-Iraqi. J Oral Dental Res 2013;23(1945):1-5.
46. Mane RJ, Choi JJE, Sharpe-Davidson WF. Tramadol as a local anaesthetic agent in dentistry: a systematic review of local and systemic adverse effects. Saudi Dent J 2021;33(8):842-52.
47. Pasternak M, Woroń J. Postępowanie w bólu poekstrakcyjnym. Ból 2020;21(1):47-52.